REMARKS

Claims 1-17 and 19-33 are currently pending. Claim 18 was previously cancelled. Claims 1, 3, 8-17, and 19-31 are currently withdrawn as being directed to non-elected subject matter. Claim 2 is amended herein. Claims 2, 4-7, and 32-33 are currently subject to examination.

The Specification has been amended herein to include SEQ ID NOs for the recited sequences, where appropriate.

Claim 2 is amended herein to recite a transcription factor decoy comprising a concatemerized double-stranded oligonucleotide molecule, wherein the concatemerized double-stranded oligonucleotide molecule is selective for a single target transcription factor and comprises at least 10 repeated copies of a domain, wherein each of said domains comprises a nucleotide sequence that acts as a transcription factor decoy for the transcription factor, wherein each of said domains comprises from about 10 to about 40 nucleotide base pairs, and wherein each of said domains is separated by an identical engineered spacer sequence comprising 10 or more non-naturally occurring nucleic acids. Support for these amendments is found, for example, at paragraphs [000366], [000368], [000372], [000402], [000421], and [000454] (specificity/selectivity of the concatemer); [00399] (nucleic acids of the spacer can be non-naturally occurring; spacer can comprise up to 10 nucleic acids or more); [00423] (genetic engineering methods can be employed to synthesize oligonucleotides, including amplification by PCR or use of a cloning vector, which methods would result in an oligonucleotide having repeated identical domain and spacer segments).

It is believed that no new matter has been added and no additional claims fees are due. Accordingly, entry of the present amendment is believed to be in order and is respectfully requested.

Amendment Requesting Entry of Sequence Listing

Applicant submits herewith a copy of the Sequence Listing in .txt format. Because the Sequence Listing is electronically filed in .txt format, it is believed that a statement as to sequence listing identity is not required, as the .txt file serves as both the paper copy and computer-readable form (CRF) copy of the Sequence Listing.

The Sequence Listing includes no new matter, in accordance with 37 C.F.R. 1.821(e), (f) or (g), or 1.825(b) or (d). Hence, Applicant respectfully requests entry of the Sequence Listing into the present application.

Claim Rejection - 35 U.C.C §103(a)

Claims 2, 4-7, 32 and 33 remain rejected under 35 U.S.C. §103(a) as being unpatentable Sharma et al., *Transcription factor decoy approach to decipher the role of NF-kappaB oncogenesis*, Anticancer Research 16(1): 61-69 (1996) (hereafter, "Sharma"), in view of Dzau et al., U.S. 2003/0186922, published October 2, 2003 (hereafter, "Dzau") and Weintraub et al., Retinoblastoma protein switches the E2F site from positive to negative element, Nature 358(6383):259-61 (1992) (hereafter, "Weintraub"). Specifically, the Examiner asserts:

> Sharma et al. teaches that the NF-kB transcription factor complex participate[s] in the induction of numerous cellular and viral genes, and the role of NF-kB in oncogenesis. Sharma et al. teaches transcription factor decoy approach to decipher the role of NF-kappaB in oncogenesis. In an effort to decipher the role of homo- vs. heterodimeric NF-kappaB in regulating tumor cell growth, Sharma et al. used a decoy approach to trap these complexes in vivo. Using double stranded phosphorothioates as a direct in vivo competitor for homo- vs heterodimeric NF-kappaB, Sharma et al. demonstrate that decoys more specific to RelA inhibit [] tumor cell growth in vitro… It is noted that double stranded NF-kB TFD comprising three end-to-end repeated copies of consensus NF-kB binding site (5'-GGG GAC TTT C-3'), which is 10 nucleotide base pairs. Sharma et al. does not explicitly teach the limitations (i) "10 end-to-end repeated copies" recited in claim 2, "15 end-to-end repeated copies" recited in claim 32, and "20 end-to-end repeated copies" recited in claim 33, and (ii) further comprising at least one tissue-specific promoter recited in claim 4.

With regard to the limitations (i) "10 end-to-end repeated copies" recited in claim 2, "15 end-to-end repeated copies" recited in claim 32, and "20 end-to-end repeated copies" recited in claim 32, Dzau et al. teaches the use of oligodeoxynucleotide decoys for the prophylactic or therapeutic treatment of diseases associated with the binding of endogenous transcription factors to genes involved in cell growth, differentiation and signaling or to viral genes. By inhibiting endogenous trans-activating factors from binding transcription regulatory regions, the decoys modulate gene expression and thereby regulating pathological processes including inflammation, intimal hyperplasia, angiogenesis, neoplasia, immune response and viral infection. Dzau et al. further teaches that the decoys contain sufficient nucleotide sequence to ensure target transcription factor binding specificity and affinity sufficient for therapeutic effectiveness.... Accordingly, cis element flanking regions may be present and concatemer oligonucleotides may be constructed with serial repetitions of the binding and/or cis element flanking sequences...

Dzau et al. teaches that the decoys may comprise a portion of a larger plasmid, including viral vectors, capable of episomal maintenance or constitutive replication in the target cell to provide longer term or enhanced intracellular exposure to the decoy sequence....

Furthermore, Weintraub et al. teaches that the role of the E2F protein in E1a promoter activity was examined in transfection assays in which a competitor plasmid containing E2F binding sites was cotransfected with the plasmid pE1aCAT, which contains the E1a promoter fused to the gene for chloramphenicol acetyltransferase (CAT)...

Based on the combined teachings of Sharma et al., Dzau et al., and Weintraub et al., the ranges of the number of end-to-end repeats present in a NF-kB transcrption factor decoy depend on the given cellular and viral genes to be inhibited in a given tissue in a desired in vitro experimental setting and/or intended in vivo therapeutic setting. The determination of the ranges of the number of end-to-end serial repeats in a NF-kB transcription factor decoy is a process of optimization.

In response to Applicant's previous arguments, the Examiner stated:

With regard to the arguments that "Weintraub is primarily directed to E2F gene promoters, rather than decoys blocking gene expression," it is noted that both Sharma et al. and Dzau et al. specifically teach decoys (i.e., verbatim) that can be used to titrate out the transcription factors that bind to a promoter. Furthermore, Weintraub et al. demonstrated that plasmids with multiple E2F transcription factor binding sites function[] as transcription factor decoy[s] that sequester[] E2F transcription factor and thus prevent[] E2F transcription factor from interacting with the E1a promoter (see Figure 4, page 262, Weintraub et al.).

Applicant traverses the rejection and requests reconsideration.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Claim 2 is amended herein to recite a transcription factor decoy comprising a concatemerized double-stranded oligonucleotide molecule, wherein the concatemerized double-stranded oligonucleotide molecule is selective for a single target transcription factor and comprises at least 10 repeated copies of a domain, wherein each of said domains comprises a nucleotide sequence that acts as a transcription factor decoy for a transcription factor, wherein each of said domains comprises from about 10 to about 40 nucleotide base pairs, and wherein each of said domains is separated by an identical engineered spacer sequence comprising 10 or more non-naturally occurring nucleic acids. Applicant submits the cited references fail to teach or suggest all limitations of claim 2, as presently amended. Specifically, Applicant finds no teaching or suggestion, *inter alia*, of an oligonucleotide comprised of repeated domains separated by identical spacers of 10 or more non-naturally occurring nucleic acids.

The instantly claimed oligonucleotide decoys are selective for a single target transcription factor. It is <u>not desirable</u> for the decoy, including both the binding domains and the intervening spacer sequences between the binding domains, to contain binding sites for other transcription factors. It is also not desirable for the spacer sequences to affect or enhance binding of the decoy, as such binding may modify selectivity of the decoy. Rather, the binding domains, spacers, and oligonucleotide concatemers decoys claimed herein are engineered so that they do <u>not</u> bind any additional sites or transcription factors in the cell, other than a single target transcription factor. In this way, selectivity of the decoy for the transcription factor can be assessed with confidence and binding by any other inadvertently-included binding site is ruled out. The spacer sequences of the instant decoys are non-naturally occurring, meaning that they do not naturally occur in portions of an endogenous promoter or human genome. One skilled in

the art would appreciate that endogenous promoters and genomic DNA often contain other binding sites that would affect binding of the oligonucleotide decoy and alter or obfuscate the assessment of decoy selectivity.

Applicant finds no teaching or suggestion in Sharma, Dzau, or Weintraub, alone or in combination, of a concatemer decoy selective for a single target transcription factor having binding domains separated by identical spacer sequences that contain 10 or more non-naturally occurring nucleotides.

The Sharma oligonucleotide contains only three transcription factor binding domains, and the two intervening sequences are neither identical nor 10 or more nucleotides in length.

The Weintraub oligonucleotide contains only two E2F binding sites, separated by a spacer of 16 nucleotides. However, Weintraub states: "To construct pSKE2F, oligonucleotides containing the E2F binding sites from the adenovirus E2a promoter (5'-AGCTTGTTTTCGCGCTTAAATTTGAGAAAGGGCGCGAAACTAGTCA-3') were synthesized such that after annealing a *Hind*III site is present on each end." (Weintraub p. 259, col. 2, last paragraph). As discussed in the concurrently submitted 1.132 Declaration by Dr. W. Keith Jones, Dr. Jones used BLAST® to compare the Weintraub sequence to the NCBI database of known sequences and obtained a match indicating the Weintraub oligonucleotide was derived from the Rous sarcoma virus terminal repeat, which acts as a promoter. Thus, although Weintraub and the Jones 1.132 Declaration differ in the ultimate origin of the sequence, it is clear that the Weintraub oligonucleotide sequence was obtained from a portion of a promoter. As such, the intervening 16 nucleotide spacer between the binding sites in the Weintraub oligonucleotide is therefore naturally-occurring, having been obtained directly from a promoter sequence.

At paragraph [0020], Dzau states:

> The decoys contain sufficient nucleotide sequence to ensure target transcription factor binding specificity and affinity sufficient for therapeutic effectiveness. For the most part, the target transcription factors will require at least six base pairs, usually at least about eight base pairs for sufficient binding specificity and affinity. Frequently, providing the decoys with flanking sequences (ranging from about 5 to 50 bp) beside the binding site enhance[s] binding affinity and/or specificity. **Accordingly, cis element flanking regions** may be present and concatemer oligonucleotides may be constructed with serial repetitions of the binding and/or cis element flanking sequences.

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). When taken as a whole, it is clear that Dzau's "flanking sequences" located beside the binding sites are cis-element flanking sequences. Cis-element flanking sequences are known in the art to be naturally-occurring sequences found in endogenous promoters or genomic DNA which serve to enhance binding of transcription factors. Applicants find no teaching or suggestion in Dzau of a spacer sequence comprised of 10 or more non-naturally occurring nucleotides. Rather, Dzau's teaching with respect to sequences in between the binding domains is limited to cis-element flanking regions.

Hence, neither Sharma, Weintraub, nor Dzau, either alone or in combination, teach or suggest an oligonucleotide decoy selective for a single target transcription factor comprised of repeated domains separated by identical spacers of 10 or more non-naturally occurring nucleic acids. Indeed, the cited references are silent with respect to the inclusion of non-naturally occurring nucleotide spacers between decoy domains. At best, Dzau discusses the inclusion of cis-element flanking sequences, which are naturally-occurring nucleotides that flank transcription factors and enhance binding. One skilled in the art, upon a reading of Dzau, would not be motivated to select spacers comprising non-naturally occurring nucleotides, since Dzau would merely guide the skilled artisan to include naturally-occurring cis-element flanking

sequences in order to enhance binding. Moreover, none of the references recognize the benefit of identical non-naturally occurring nucleotide spacers with respect to designing a selective decoy.

The Examiner has acknowledged that the primary reference, Sharma, fails to teach 10, 15, or 20 repeated copies of the binding domains in a single concatemer, and applies Dzau for the asserted teaching of serial repetitions of the binding and/or cis-element flanking sequences. However, Applicant submits that, even if the oligonucleotide of Sharma were concatemerized as the Examiner has suggested, the resulting concatemer still would not have all the claimed features of the concatemer of claim 2. Namely, if multiple copies of the Sharma construct were joined end to end, the resulting oligonucleotide would not be selective for a single transcription factor. Rather, as discussed by Dr. W. Keith Jones in the attached 1.132 Declaration, if the Sharma construct were joined end to end to create a concatemer according to the instant claims, the new joint between the copies would introduce new binding sites for Stat 1/3 and Stat 5/6 (see paragraph 4 of the Jones 1.132 Declaration). As such, a concatemer of the Sharma construct would not be selective for a single transcription factor, as claimed in instant claim 2.

Applicant further notes the construct of Weintraub is not selective for a single transcription factor. As discussed in the Jones 1.132 Declaration, the Weintraub construct has a binding site for Pax-6, which overlaps one of the E2F sites, and a site for CP2, which overlaps a second E2F binding site (see paragraph 5 of the Jones 1.132 Declaration). Moreover, if the Weintraub decoy were concatemerized, the joint between the copies would introduce new binding sites for GCN4, JunB/D, and Opaque-2 (see paragraph 6 of the Jones 1.132 Declaration). Hence, a concatemer of the Weintraub construct would not be selective for a single transcription factor, as claimed in instant claim 2.

Finally, Applicant reaffirms that none of the references, either alone or in combination, teach or suggest a concatemer of the length instantly claimed herein. The length of the instantly claimed concatemers confers several advantageous properties: an increased half-life of the decoy within a cell, as well as increased efficacy of each molecule, since each decoy contains multiple copies of the binding site (see paragraph [0034] of the Specification as filed). Neither Sharma nor Weintraub contemplated concatemer decoys, and the Examiner has applied Dzau for the asserted suggestion of forming a concatemer. However, Applicant again notes that Dzau expressly states that his decoys are "nonreplicative oligonucleotides fewer than 100 bp, usually fewer than 50 bp" (see paragraph [0021] of Dzau). Further, Dzau does not exemplify any oligonucleotide having a sequence longer than 30 bp (see Dzau sequence listing). Applicant submits none of the cited references, either alone or in combination, teach or suggest a concatemer of the length and selectivity currently claimed. And, as noted above, the stability and efficacy of the instantly claimed longer concatemers confer advantages not present in the shorter decoys envisioned by Sharma, Weintraub, or Dzau, either alone or in combination.

In view of the foregoing, Applicant respectfully submits that the rejection of claims 2, 4-7, 32 and 33 under 35 U.S.C. §103(a) as being unpatentable over Sharma in view of Dzau and Weintraub is overcome. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

It is believed that the present Amendment involves the introduction of no new matter and represents a complete response to the Office Action dated November 14, 2011. Applicant therefore respectfully requests entry of the present Amendment, reconsideration, withdrawal of the rejection under 35 U.S.C. §103, and an early allowance of claims 2, 4-7, and 32-33.

It is believed that no additional fees are required, but in the event this is incorrect, please charge any additional fees required in connection with the present Amendment to Deposit Account No. 04-1133.

Respectfully submitted,

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